

#12

Commissioner of Patents and Trademarks  
Box Patent Ext.  
Washington, D.C. 20231

\$200  
75c REFUND SCHEDULED  
JUN 5 1987

Dear Sir:

Pursuant to the provisions of 35 U.S.C. 156, Mead Johnson & Company, (hereinafter "Mead Johnson"), as a wholly-owned subsidiary of Bristol-Myers Company, hereby requests a two year extension of the term of U.S. Patent 4,182,763, i.e., an extension of the patent expiration date from January 8, 1997 to January 8, 1999. Mead Johnson is the assignee of U.S. Patent 4,182,763 from the inventors, all of whom were employees of Mead Johnson at the time of the invention. Agreements between Mead Johnson and the inventors vested all patent rights with Mead Johnson, as a result of which Mead Johnson is the owner of record and entitled to all rights of patent ownership including the right to apply for extension of the patent. U.S. Patent 4,182,763 covers the use of 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride known generically as buspirone hydrochloride. Buspirone hydrochloride is the "approved product" and is marketed by Mead Johnson under the brand name BUSPAR. Mead Johnson's parent, Bristol-Myers Company, is the holder of approved New Drug Application 18-731 (hereinafter called the "NDA") for BUSPAR. The NDA was approved by the FDA on September 29, 1986, in accordance with 21 U.S.C. 355(c), and permits the commercial marketing and use of BUSPAR in the management of anxiety disorders and the short term relief of the symptoms of anxiety. The FDA's approval of NDA 18-731 constituted the first permitted commercial marketing or use of product buspirone hydrochloride under 21 U.S.C. 355(c)(1).

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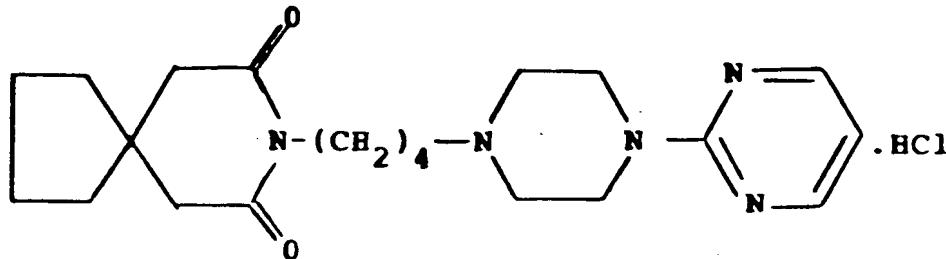
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Section 1

Complete identification of the approved product

The approved product BUSPAR (generic name "buspirone hydrochloride") has:

a) the structural formula,



b) the empirical formula,  $C_{21}H_{31}N_5O_2 \cdot HCl$

c) molecular weight of 422.0

d) the chemical name, 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro [4.5]decane-7,9-dione hydrochloride.

Section 2

Complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

Pursuant to Section 505(c)(1)(A) of the Federal Food, Drug and Cosmetic Act, (21 USC 355(c)(1)(A)), NDA 18-731 was approved and BUSPAR received permission for commercial marketing on September 29, 1986. While IND 8705 became effective on April 16, 1972, the applicable review period for the use claimed relative to BUSPAR as an antianxiety agent in U.S. Patent 4,182,763 began on October 22, 1976.

Prior to October 22, 1976, buspirone hydrochloride was studied for a different use than that claimed in the patent referred to above. A chronology of the regulatory review period is provided in Sections 9 and 10.

### Section 3

Identification of the date on which the product received permission for commercial marketing.

The BUSPAR NDA (#18-731) was approved on September 29, 1986 pursuant to Section 505(c) of the Federal Food, Drug and Cosmetic Act. Buspirone hydrochloride is the only active ingredient of the approved product and has not been previously approved for commercial marketing or use.

### Section 4

This application is being submitted within the sixty-day period provided by 35 U.S.C. 156(d)(1) since approval was granted on September 29, 1986 and the sixty-day period will lapse on November 28, 1986.

### Section 5, 6

Complete identification of the patent. Copy of the patent.

The patent for which an extension is sought is U.S. Patent 4,182,763. It issued on January 8, 1980, on the application filed by George P. Casten, Gordon R. McKinney, Roger E. Newton, E. Crosby Tompkins, and John H. Weikel, Jr., on May 22, 1978. A copy of U.S. Patent 4,182,763, which is for BUSPIRONE ANTI-ANXIETY METHOD is provided as Attachment 1. U.S. Patent 4,182,763 names Mead Johnson as the Assignee.

Section 7

Copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

A copy of a certificate for correction of inventorship issued by the United States Patent and Trademark Office on March 18, 1986 is provided as Attachment 2. This certificate was requested to correct the inventorship of the patent by adding John E. Gajewski as one of the inventors.

A copy of a certificate of correction of Office mistake issued by the United States Patent and Trademark Office on July 8, 1986 is provided as Attachment 3. This certificate was requested to correct a mistake appearing in claim 5 and believed to have occurred during the printing of the patent.

*(Section 8 begins on the next page)*

Section 8

Statement that the patent claims a method of using the approved product

U.S. Patent 4,182,763 claims a method of using the approved product:

Claim 1 of U.S. Patent 4,182,763 covers a method of using the approved product BUSPAR in the palliative treatment of neurosis in which anxiety symptoms are prominent;

Claim 2 covers the use of BUSPAR by the oral route according to the method of claim 1;

Claim 3 covers the use of BUSPAR in patients suffering from anxiety neurosis according to the method of claim 2;

Claim 4 covers the use of BUSPAR in patients suffering from anxiety neurosis with depressive symptoms according to the method of claim 2;

Claim 5 (as corrected) covers an adult daily dose from 10 mg. to 60 mg. according to the method of claims 2, 3, or 4;

Claim 6 covers a daily divided dose administered b.i.d. according to the method of claim 5;

Claim 7 covers a daily divided dose administered t.i.d. according to the method of claim 5;

Claim 8 covers a maximum total dose of up to about 100 mg. according to the method of claim 2;

Claim 9 covers an adult therapeutic daily dose of from 20 mg. to 30 mg. according to the method of claims 2, 3, or 4.

*(Section 9 begins on the next page)*

Section 9

Relevant dates and information pursuant to 35 U.S.C.  
156(g) to enable a determination of the applicable  
regulatory review period:

October 22, 1976

Effective date of IND Applica-  
tion No. 8705 for use as an  
antianxiety agent.\*

December 15, 1982

Submittal date of NDA No. 18-731

September 29, 1986

NDA approval date

\* IND Application No. 8705 became effective on April 16, 1972. However, the applicable review period for the use claimed relative to BUSPAR as an antianxiety agent (U.S. Patent No. 4,182,763) actually began on October 22, 1976.

*(Section 10 begins on the next page)*

Section 10

Brief description of the activities undertaken by the applicant during the applicable regulatory review period with respect to the approved product and significant dates applicable to such activities.

Bristol-Myers Company, on behalf of Mead Johnson & Company, undertook the development of this product to establish, by adequate and well-controlled clinical trials, its safety and effectiveness in the treatment of anxiety disorders and the short-term relief of symptoms of anxiety. Since this product was a new drug as defined under Section 201(p) of the Food, Drug and Cosmetic Act, an approved NDA for the product was required to be obtained under section 505(b) of the Food, Drug and Cosmetic Act prior to its commercial marketing.

An exemption under subsection(1) of Section 505 of the Food, Drug and Cosmetic Act was submitted to the FDA on October 22, 1976, requesting permission to evaluate BUSPAR in patients with anxiety symptoms. No request was made by the FDA that the sponsor continue to withhold or to restrict use of the drug in human subjects. The following is a chronology of activity that ensued:

October 22, 1976

Start-up of Clinical Study #657. This is the first clinical study protocol to evaluate BUSPAR in the treatment of anxiety submitted to FDA.

November 9, 1976

Phase II clinical testing initiated.

December 21, 1976	Start-up of Clinical Study #684. Clinical study protocol for this sleep study submitted to FDA.
March 15, 1977	Study report on metabolic disposition of radio labeled buspirone in man submitted to FDA (Study #599).
June 1, 1977	Start-up of Clinical Study #764. Clinical study protocol for this clinical efficacy study submitted to FDA.
June 16, 1977	Results of 2 year rat tumorigenicity study submitted to FDA.
June 9, 1978	Results of 18-month mouse tumorigenicity study submitted to FDA.
June 21, 1978	End Phase II meeting with FDA.
August 6, 1978	Response provided to FDA concerning chemistry questions raised in FDA letter of July 10, 1978.
November 28, 1978	Start-up of Clinical Study #1003. Clinical study protocol for this functional impairment study submitted to FDA.

March 26, 1979

Start-up of Clinical Studies #994, 996 and 1000. Clinical study protocols for these clinical efficacy studies submitted to FDA.

April 2, 1979

Start-up of Clinical Study #995. Clinical study protocol for this clinical efficacy study submitted to FDA.

April 4, 1979

Start-up of Clinical Studies #1012 and 1029. Clinical study protocols for these clinical efficacy studies submitted to FDA.

April 19, 1979

Start-up of Clinical Study #1041. Clinical study protocol for this clinical efficacy study submitted to FDA.

May 21, 1979

Start-up of Clinical Study #1032. Clinical study protocol for this clinical efficacy study submitted to FDA.

July 6, 1979

Start-up of Clinical Study #1048. Clinical study protocol for this clinical efficacy study submitted to FDA.

July 25, 1979

Start-up of Clinical Study #1049. Clinical study protocol for this clinical efficacy study submitted to FDA.

JANUARY 8, 1980

PATENT 4,182,763 ISSUED.

March 18, 1980

Meeting with FDA regarding drug abuse/physical dependence/scheduling considerations.

June 27, 1980

Start-up of Clinical Study #1183. Clinical study protocol for this clinical efficacy study submitted to FDA.

September 2, 1980

Start-up of Clinical Study #1207. Clinical study protocol for this functional impairment study submitted to FDA.

September 24, 1980

Meeting with FDA Drug Abuse Staff.

October 30, 1980

Meeting with FDA regarding biopharmaceutics issues.

November 6, 1980

Start-up of Clinical Study #1261. Clinical study protocol for this bioavailability study submitted to FDA.

January 30, 1981

Start-up of Clinical Study #1290. Clinical study protocol for this functional impairment study submitted to FDA.

March 31, 1981

Meeting with FDA regarding drug scheduling.

May 5, 1981

Start-up of Clinical Study #1324.  
Clinical study protocol for this  
neuroendocrine study submitted to  
FDA.

July 30, 1981

Meeting with FDA regarding biopharmaceutics - assay methodology and data analysis.

August 28, 1981

Start-up of Clinical Study #1367.  
Clinical study protocol for this abuse potential study submitted to FDA.

November 10, 1981

Pre NDA submission meeting with FDA.

December 23, 1981

Start-up of Clinical Study #1380.  
Clinical study protocol for abuse potential study submitted to FDA.

March 30, 1982

Chemical - Manufacturing - Control and Preclinical Pharmacology and Toxicology sections of BUSPAR NDA submitted to FDA.

June 10, 1982

Provided FDA information requested by Reviewing Chemist.

September 27, 1982

Start-up of Clinical Study #1480.  
Clinical study protocol for this neuroendocrine study submitted to FDA.

DECEMBER 15, 1982

SUBMISSION OF BUSPAR NDA #18-731 TO  
FDA.

January 19, 1983

Letter to FDA regarding BUSPAR drug class classification.

February 4, 1983

Provided FDA additional chemistry and biopharmaceutics information.

March 10, 1983

Provided FDA information requested by Biopharmaceutics Reviewer.

March 21, 1983

Provided FDA information requested by Reviewing Chemist.

March 31, 1983

Letter to FDA regarding BUSPAR drug classification.

April 28, 1983

Submission to FDA consisting of copies of published papers, preclinical reports and an update on human safety aspects.

May 10, 1983

Letter requesting meeting with FDA regarding status of NDA review.

May 16, 1983

Provided FDA clinical final reports for Studies #439, #532, and #606.

May 16, 1983

Provided FDA information requested by Reviewing Chemist.

June 13, 1983

Provided FDA updated pharmacologic summary and additional animal toxicology information.



December 2, 1983      Information on an alternative tablet shape was provided to FDA.

December 2, 1983      Final biopharmaceutics report for Study #1490 was provided to FDA.

December 16, 1983      Letter for FDA records confirming incorporation into the NDA of our submission of August 6, 1983 in which additional statistical information was provided directly to the Reviewing Statistician for clinical Studies #994 and #995.

January 18, 1984      Letter from Ganes Chemicals, Inc. regarding Drug Master File.

January 19, 1984      Provided FDA requested information on Drug Master File.

February 17, 1984      Letter to FDA provided suggested dates for meeting with Biopharmaceutics Staff.

February 27, 1984      FDA letter requesting additional information on biopharmaceutics questions.

March 21, 1984      Provided FDA additional biopharmaceutics data.

March 28, 1984      Meeting with FDA staff regarding biopharmaceutics issues.

April 11, 1984

Provided FDA outline for a proposed animal study to Reviewing Pharmacologist.

July 5, 1984

Provided FDA requested information on plasma levels of a BUSPAR metabolite.

July 5, 1984

Response to FDA letter of February 27, 1984 regarding biopharmaceutics issues.

July 5, 1984

Provided FDA additional information on possible neuroendocrine effects of BUSPAR.

July 19, 1984

Information on an alternative BUSPAR tablet shape was provided to FDA.

August 9, 1984

Provided FDA an abstract of a paper on animal pharmacology of BUSPAR.

September 6, 1984

Revised draft of the proposed labeling for BUSPAR was provided to FDA.

September 27, 1984

FDA was provided with a safety update based on ongoing BUSPAR clinical studies and a revised draft of the proposed package insert.

December 21, 1984

Letter to Reviewing Chemist regarding alternative tablet shape.

January 11, 1985

Additional packaging specifications for BUSPAR were provided to FDA.



January 20, 1986

Comprehensive safety update for  
BUSPAR submitted to FDA as an  
amendment.

February 3, 1986

Addendum to safety update submitted  
to FDA.

February 6, 1986

Letter received from FDA stating that  
the safety update was considered a  
major amendment by regulation, that  
an additional 90 days was established  
for its review, and that the new due  
date is April 23, 1986.

February 26, 1986

Provided FDA requested additional  
information for clinical study #1012.

March 3, 1986

Letter addressed to FDA Medical  
Reviewer containing data on patient  
discontinuations for safety update.

March 11, 1986

Letter addressed to FDA Medical  
Reviewer enclosing draft statement  
concerning overall adverse event rate  
for inclusion in labeling.

March 13, 1986

Meeting date requested to discuss  
labeling.

March 17, 1986

Provided FDA requested information  
regarding clinical study #246 and  
copy of final study report for study  
#246.

March 17, 1986

FDA records disclose a duplicate  
3/17/86 submission in their files.

March 26, 1986

Letter to Medical Officer which provides a copy of March 17, 1986 cover letter regarding clinical study #246.

March 26, 1986

Letter to FDA provided information on the status of BUSPAR patents.

April 1, 1986

Additional information provided to FDA on BUSPAR patents.

April 1, 1986

Letter addressed to FDA requesting a copy of the draft labeling proposed for BUSPAR.

June 17, 1986

Provided requested additional statistical analyses for clinical studies #994, #1802, and #2044.

June 19, 1986

Provided FDA requested additional clinical information on prior benzodiazepine use in patients for study #994, #1802, and #2044.

June 25, 1986

Provided to the Reviewing Statistician requested information regarding clinical study #1012.

July 9, 1986

Letter to FDA listing the 13 countries in which the registration of BUSPAR was approved.

July 17, 1986

Date of FDA letter stating that NDA application was approvable.

July 22, 1986

Letter informing the FDA that Bristol-Myers Company will file an amendment to the pending BUSPAR NDA.

August 5, 1986

Response to FDA letter of July 17, 1986 and a request for a meeting with FDA staff, if necessary, to resolve labeling issues.

August 19, 1986

Submission to FDA of several key publications and internal reports to support applicant's position that BUSPAR affects neurotransmitter systems other than the dopaminergic system.

August 20, 1986

Submission to FDA of: (a) summary information for six clinical studies dealing with effects of BUSPAR on depressive patients symptomatology; (b) two papers describing the effects of BUSPAR on patients with Parkinson's disease; and (c) a report describing the use of BUSPAR on a long term basis.

August 22, 1986

Submission to FDA of final safety update.

August 29, 1986

Meeting between FDA and Bristol-Myers Company representatives pertaining to labeling for BUSPAR. On occasion of that meeting, handed to FDA representatives two corrected pages to the safety update previously provided to FDA on August 22, 1986 and memorandum dated August 28, 1986 relating to the two corrected pages.

September 3, 1986

Letter to FDA dated September 2, 1986 provided final printed labeling and commitment to conduct the Phase IV studies requested by the FDA.

September 3, 1986

Additional information provided to FDA on dissolution specification for BUSPAR tablets.

September 4, 1986

Submission to FDA of a report on the safety and efficacy of BUSPAR in the elderly.

September 5, 1986

Provided FDA requested information on modal total daily dose of BUSPAR in the elderly.

September 29, 1986

FDA approval letter for NDA #18-731 received, granting permission for commercial marketing pursuant to Section 505(c)(1)(A) of the Federal Food, Drug and Cosmetic Act.

During the entire period from October 22, 1976 through December 14, 1982, the data generated on this product were under preparation for submission to FDA in support of the NDA. The NDA review period lasted from December 15, 1982 through September 29, 1986, with due diligence on the part of the sponsor during the entire regulatory review period.

*(Section 11 begins on the next page)*

Section 11

Patent eligibility and the length of extension claimed.

U.S. Patent 4,182,763 is eligible for extension for 2 years since:

- (a) It claims use of the approved human drug product, BUSPAR;
- (b) The term of said patent has never been previously extended;
- (c) The application is submitted by the owner of the patent, Mead Johnson & Company;
- (d) The product, BUSPAR, has been subject to regulatory review prior to commercial marketing or use;
- (e) The product received permission for commercial marketing or use on September 29, 1986 and the application has been submitted within 60 days from that date;
- (f) The term of the patent has not expired prior to this date of application; and
- (g) No other patent term has been extended for the same regulatory review period for this product.

The length of extension claimed is the lesser of 2 years or the following calculated period of time:

Testing period began:	October 22, 1976
Patent issued:	January 8, 1980
NDA submitted:	December 15, 1982
NDA approved:	September 29, 1986

The testing period would equal the time between October 22, 1976 and December 15, 1982, less the period of time prior to the patent issuance (January 8, 1980), or 1,072 days.

The approval period would equal the time between December 15, 1982 and September 29, 1986 or 1,382 days.

The total extension would equal  $1/2 \times 1,072 + 1,382$  or 1,918 days. Since this is greater than 2 years, the extension sought is for a 2 year period.

#### Section 12

##### Duty of Disclosure

The applicant hereby acknowledges his duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to this application for patent extension.

#### Section 13

The prescribed fee (\$750.00) for receiving and acting upon the application for extension is attached. Inquiries and correspondence should be addressed to:

Isaac Jarkovsky, Esq.  
Assistant General Counsel-Patents  
Bristol-Myers Company  
345 Park Avenue  
New York, New York 10154  
Telephone: 212-546-3653

Declaration

The undersigned, Vice President and Counsel of Mead Johnson & Company, applicant for extension of U.S. Patent 4,182,763, hereby avers that he is an authorized official of Mead Johnson & Company and:

1. Has reviewed and understands the contents of the application being submitted pursuant to 35 U.S.C. 156;
2. Believes U.S. Patent 4,182,763 is subject to extension pursuant to A of the Guidelines for Extension of Patent Term issued by the U.S. Patent and Trademark Office on September 25, 1984 (Guidelines), and 35 U.S.C. 156;
3. Believes an extension for 2 years, the length claimed, is fully justified under 35 U.S.C. 156; and
4. Believes the patent for which the extension is being sought meets the conditions for extension of the term of the patent as set forth in B of the Guidelines.

Sincerely,



Robert N. Endries  
Robert N. Endries  
Vice President and Counsel  
Mead Johnson & Company

# United States Patent [19]

Casten et al.

[11] 4,182,763

[45] Jan. 8, 1980

[54] **BUSPIRONE ANTI-ANXIETY METHOD**

3,976,776 8/1976 Wu et al. .... 424/251

[75] Inventors: George P. Casten; Gordon R. McKinney; Roger E. Newton; E. Crosby Tompkins, all of Evansville; John H. Welkel, Jr., Mt. Vernon, all of Ind.

## OTHER PUBLICATIONS

Wu et al., J. Med. Chem. 15, (1972), pp. 477-479.  
Allen et al., Arzneim-Forsch, 24, No. 6, 917-992 (1974).  
Sathancethan et al., Current Therapeutic Research, 18, (5), 701-705 (1975).

[73] Assignee: Mead Johnson & Company, Evansville, Ind.

Primary Examiner—Stanley J. Friedman  
Attorney, Agent, or Firm—R. E. Carnahan; R. H. Uloth

[21] Appl. No.: 908,597

## [57] ABSTRACT

[22] Filed: May 22, 1978

Buspirone hydrochloride is an effective anti-anxiety agent for the palliative treatment of neurotic patients in which symptoms of anxiety are predominant at doses which are without observable effect in either normal individuals or psychotic patients.

[51] Int. Cl.: A61K 31/505

9 Claims, No Drawings

[52] U.S. Cl. .... 424/251

[58] Field of Search .... 424/251

## [56] References Cited

## U.S. PATENT DOCUMENTS

3,717,634 2/1973 Wu et al. .... 260/256.4 N

UNITED STATES PATENT AND TRADEMARK OFFICE

Certificate

Patent No. 4,182,763

Patented January 8, 1980

On petition requesting issuance of a certificate for correction of inventorship pursuant to 35 USC 256, it has been found that the above-identified patent, through error and without any deceptive intent, improperly sets forth the inventorship. Accordingly, it is hereby certified that the correct inventorship of this patent is George P. Cästen, Gordon R. McKinney, Roger E. Newton, E. Crosby Tompkins, John H. Weikel, Jr. and John E. Gajewski.

Signed and Sealed this Eighteenth Day of March 1986.



*Office of the Deputy Assistant  
Commissioner for Patents.*



Attachment 2

UNITED STATES PATENT AND TRADEMARK OFFICE  
CERTIFICATE OF CORRECTION

PATENT NO. : 4,182,763

DATED : January 8, 1980

INVENTOR(S) : George P. Casten et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 8, line 5, Claim 5, delete "2, 3 or 5" and insert  
-- 2, 3 or 4 --.



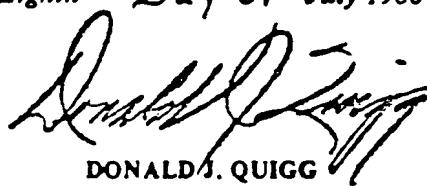
Attest:

Priscilla A. Huller

Attesting Officer

Signed and Sealed this

Eighth Day of July 1986

  
DONALD J. QUIGG

Commissioner of Patents and Trademarks